(b) [efficient transduction of] efficiently transducing said vectors into a number of identical eukaryotic cells in such a way that each cell expresses either a single ribonucleic acid and possibly peptide [is expressed] encoded by the DNA sequence to be examined or a limited number of different ribonucleic acids and peptides [are expressed by each cell] encoded by DNA sequences to be examined,

(c) screening [of] said transduced cells to see whether some of them have [changed a certain] altered a preselected phenotypic trait, and

(d) [selection] selecting and cloning [of said changed] cells which have altered the preselected phenotypic trait, [characterized in that]

wherein the pool of appropriate vectors in step (a) [contain] contains totally or partly random DNA sequences selected from the group consisting of:

i) synthetic totally random DNA sequences;

ii) synthetic random DNA sequences[, in which restrictions upon the randomness may be introduced for the purpose of limiting

the number of available sequences and/or for the introduction of post-translational modifications of expressed peptides] wherein stop codons are absent;

(iii) synthetic DNA sequences which encode random amino acid sequences with an even distribution of amino acids;

(iv) synthetic DNA sequences defined in (i), (ii), or (iii) separated by codons which enable specific post translational modifications of all expressed peptides or which encode anchor residues;

v) [iii)] synthetic [random] DNA sequences [like] defined in (i), [or] (ii), (iii), or (iv) coupled to coding sequences of purification tags in order to facilitate the purification and identification of expressed peptides; and

vi) [iv] synthetic [random] DNA sequences [like] defined in (i), (ii), [or] (iii), (iv), or (v) coupled to or inserted into the coding sequence of a protein;

and [that either] wherein

(e) the vector DNA in the phenotypically [changed] altered cells is isolated and sequenced, and the sequences of the

[biologically active] ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are deduced from the sequenced vector DNA;

and/or

(f) the [biologically active] ribonucleic acids or peptides [expressed in the phenotypically changed cells] effecting alteration of the preselected phenotypic trait are used directly for isolation of a ligand molecule to said ribonucleic [acid] acids or [peptide] peptides.

Claim 2, line 1, delete "A" and insert --The--;

line 2, delete "introduced" and insert --inserted--;

line 3, after "protein" insert --amino acid sequence--;

lines 3-4, delete ",preferably a F(ab) fragment or an antibody molecule".

Claim 3, line 1, delete "A" and insert --The--;

lines 2-3, delete "amino acid sequences of the random peptide library are encoded by";

line 3, delete "/oligonucleotides" and insert --are--;

line 4, delete "codon split synthesis" and insert --random codon synthesis--.

Claim 4, line 1, delete "A" and insert --The--;

line 2, delete "amino acid sequences of the random peptide library are encoded by";

line 3, delete "/oligonucleotides" and insert --are--.

5. (Amended) [A] The method according to claim 1 in which the synthetic random DNA sequences are introduced into the expression vector in step (a) by [the principle of] site directed PCR-mediated mutagenesis hereby ensuring the complexity of the [library] totally ~~or partly~~ random DNA sequences.

6. (Amended) [A] The method according to claim 5 in which [3'-5' exonuclease trimming of PCR product 3' ends is used for] optimal combining efficiencies of two [such] PCR products is achieved by trimming 3' ends of PCR products with a 3'-5' exonuclease.

7. (Amended) [A] The method according to claim 1, in which [temperature-cycling ligation is used for optimal] ligation of DNA fragment into a vector is optimized by performing temperature cycling ligation in step (a), thereby maintaining a high diversity of the [library] totally ~~or partly~~ random DNA sequences for transfection into packaging cells.

Claim 8, line 1, delete "A" and insert --The--.

9. (Amended) [A] The method according to claim 1, in which the random DNA sequences are introduced into the eukaryotic cells by the use of an appropriate viral [vectors] vector selected from [e.g.] a retrovirus vector [or] and a vaccinia virus vector.

Claim 10, line 1, delete "A" and insert --The--.

Claim 11, line 1, delete "A" and insert --The--.

Claim 12, line 1, delete "A" and insert --The--.

Claim 13, line 1, delete "A" and insert --The--.

Claim 14, line 1, delete "A" and insert --The--;

line 3, delete "the".

Claim 15, line 1, delete "A" and insert --The--;

line 3, delete "and used for" and insert --followed by--;

lines 3-4, delete "new target" and insert --further--.

16. (Amended) [A] The method according to claim 9, in which the viral titer of retroviral packaging cell lines is increased by

transient transfection with a functional tRNA gene corresponding to [the] a primer binding site(PBS) in the vector.

17. (Amended) [A] The method according to claim 9, [in which] comprising transfecting a packaging cell line constructed from a vector [expressing a] encoding one single transcript [translating] which translates into [the three polyproteins/proteins,] gag-pol, a [drug resistance gene] selectable marker, and [the] env [gene is used].

18. (Amended) [A] The method according to claim 9, [in which] comprising transfecting a semi-packaging cell line with a corresponding minivirus/vector thereby enabling vector expression after transduction of cells rather than after transfection of cells [is used].

Claim 19, line 1, delete "A" and insert --The--;

lines 3-4, delete "such as e.g. glycosylation sites and anchor residues".

20. (Amended) [A] The method according to claim 1, in which the [biologically active peptide or protein] peptide effecting the phenotypic alteration also contains a purification tag [enabling the] which enables direct isolation of the [biologically active protein] peptide as well as of the [target protein causing the biological activity] molecule with which the peptide interacts.

21. (Amended) [A] The method according to claim 1, in which appropriate signal peptides, other leader molecules or recognition sequences [also] are also encoded by the [introduced DNA in such a way that they are fused to the] vectors in the form of fusion partners to expressed random peptides[,] or to [the] expressed proteins containing [the] random peptide sequences, thereby enabling [these to be directed towards] translocation of these to defined cellular compartments.

Claim 22, line 1, delete "A" and insert --The--;

line 2, delete "introduced" and insert --inserted--;

line 3, delete "fused" and insert --linked--;

line 4, delete "library".

Claim 23, line 1, delete "A" and insert --The--.

24. (Amended) [A] The method acccrding to claim 22, in which the protein is [derived wholly or partly from the] a heavy and/or light chain of an antibody molecule, or a part thereof.

25. (Amended) [A] The method according to claim 1, [which is used for identification of T cell epitopes] wherein screening in step (c) identifies presence of T-cell epitopes bound to MHC molecules on the surface of the transduced cells.

26. (Amended) [A] The method according to claim 1, [which is used for identifying biologically active peptides which regulate cell surface expression of proteins] wherein the preselected phenotypic trait is cell surface expression of a protein.

Kindly cancel claims 27-29 without prejudice or disclaimer.

Kindly add claims 30-42 as follows:

--30. The method according to claim 1, wherein the synthetic DNA sequences each encode 6-10 random amino acids.

31. The method according to claim 30, wherein the synthetic DNA sequences each encode 8-9 random amino acids.

32. A method for identification of biologically active nucleic acids or peptides or their cellular ligands, which comprises the steps of

(a) producing a pool of appropriate vectors each containing a DNA sequence to be examined,

(b) efficiently transducing said vectors into a number of identical eukaryotic cells in such a way that each cell expresses either a single ribonucleic acid and possibly peptide encoded by the DNA sequence to be examined or a limited number of different ribonucleic acids and peptides encoded by DNA sequences to be examined,

(c) screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, wherein the screening method is different from capture of the expressed ribonucleic acid(s) or peptide(s) with a ligand, and

(d) selecting and cloning cells which have altered the preselected phenotypic trait,

wherein the pool of appropriate vectors in step (a) contains totally or partly random DNA sequences selected from the group consisting of:

i) synthetic totally random DNA sequences;

ii) synthetic random DNA sequences wherein stop codons are absent;

iii) synthetic DNA sequences which encode random amino acid sequences with an even distribution of amino acids;

iv) synthetic DNA sequences defined in (i), (ii), or (iii) separated by codons which enable specific post-translational modifications of all expressed peptides or which encode anchor residues;

v) synthetic DNA sequences defined in (i), (ii), (iii), or (iv) coupled to coding sequences of purification tags in order to facilitate the purification and identification of expressed peptides; and

vi) synthetic DNA sequences defined in (i), (ii), (iii), (iv), or (v) coupled to or inserted into the coding sequence of a protein;

and wherein

(e) the vector DNA in the phenotypically altered cells is isolated and sequenced, and the sequences of the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are deduced from the sequenced vector DNA;

and/or

(f) the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are used directly for isolation of a ligand molecule to said ribonucleic acids or peptides.

33. A method for identification of biologically active nucleic acids or peptides or their cellular ligands, which comprises the steps of

(a) producing a pool of appropriate vectors each containing a DNA sequence to be examined,

(b) efficiently transducing said vectors into a number of identical eukaryotic cells in such a way that each cell expresses either a single ribonucleic acid and possibly peptide encoded by the DNA sequence to be examined or a limited number of different ribonucleic acids and peptides encoded by DNA sequences to be examined,

(c) screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, where alteration of the preselected phenotypic trait in a cell is ascribable to the expressed ribonucleic acid(s) or peptide(s) affecting biological functions of the cell which have influence on the preselected phenotypic trait, and

(d) selecting and cloning cells which have altered the preselected phenotypic trait,

wherein the pool of appropriate vectors in step (a) contains totally or partly random DNA sequences selected from the group consisting of:

i) synthetic totally random DNA sequences;

ii) synthetic random DNA sequences wherein stop codons are absent;

iii) synthetic DNA sequences which encode random amino acid sequences with an even distribution of amino acids;

iv) synthetic DNA sequences defined in (i), (ii), or (iii) separated by codons which enable specific post-translational modifications of all expressed peptides or which encode anchor residues;

v) synthetic DNA sequences defined in (i), (ii), (iii), or (iv) coupled to coding sequences of purification tags in order to facilitate the purification and identification of expressed peptides; and

vi) synthetic DNA sequences defined in (i), (ii), (iii), (iv), or (v) coupled to or inserted into the coding sequence of a protein;

and wherein

(e) the vector DNA in the phenotypically altered cells is isolated and sequenced, and the sequences of the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are deduced from the sequenced vector DNA;

and/or

(f) the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are used directly for isolation of a ligand molecule to said ribonucleic acids or peptides.

34. A method for identification of T-cell epitopes, which comprises the steps of:

(a) producing a pool of appropriate vectors each containing a DNA sequence to be examined,

(b) efficiently transducing said vectors into a number of identical eukaryotic cells in such a way that each cell expresses either a single peptide encoded by the DNA sequence to be examined or a limited number of different peptides encoded by DNA sequences to be examined,

(c) screening said transduced cells to see whether some of them have altered a preselected phenotypic trait which indicates that peptide(s) encoded by DNA sequence(s) are bound to MHC molecules on the surface of the transduced cells, and

(d) selecting and cloning cells which have altered the preselected phenotypic trait,

wherein the pool of appropriate vectors in step (a) contains totally or partly random DNA sequences selected from the group consisting of:

i) synthetic totally random DNA sequences;

ii) synthetic random DNA sequences wherein stop codons are absent;

iii) synthetic DNA sequences which encode random amino acid sequences with an even distribution of amino acids;

iv) synthetic DNA sequences defined in (i), (ii), or (iii) containing interspersed codons which allow specific post-translational modifications of all expressed peptides or which encode anchor residues;

v) synthetic DNA sequences defined in (i), (ii), (iii), or (iv) coupled to coding sequences of purification tags in order to facilitate the purification and identification of expressed peptides; and

vi) synthetic DNA sequences defined in (i), (ii), (iii), (iv), or (v) coupled to or inserted into the coding sequence of a protein;

and wherein

(e) the vector DNA in the phenotypically altered cells is isolated and sequenced, and the sequences of the peptides effecting alteration of the phenotype of the cell(s) are deduced from the sequenced vector DNA;

and/or

(f) the peptides effecting alteration of the phenotype of the cell(s) are used directly for isolation of a ligand molecule to said ribonucleic acids or peptides.

35. A method for identification of biologically active nucleic acids or peptides which regulate cell surface expression of a protein or their cellular ligands, which comprises the steps of

(a) producing a pool of appropriate vectors each containing a DNA sequence to be examined,

(b) efficiently transducing said vectors into a number of identical eukaryotic cells in such a way that each cell expresses either a single ribonucleic acid and possibly peptide encoded by the DNA sequence to be examined or a limited number of different ribonucleic acids and peptides encoded by DNA sequences to be examined,

(c) screening said transduced cells to see whether some of them have altered cell surface expression of a protein of the cell, and

(d) selecting and cloning cells which have altered the cell surface expression of the protein,

wherein the pool of appropriate vectors in step (a) contains totally or partly random DNA sequences selected from the group consisting of:

i) synthetic totally random DNA sequences;

ii) synthetic random DNA sequences wherein stop codons are absent;

iii) synthetic DNA sequences which encode random amino acid sequences with an even distribution of amino acids;

iv) synthetic DNA sequences defined in (i), (ii), or (iii) containing interspersed codons which allow specific post translational modifications of all expressed peptides or which encode anchor residues;

v) synthetic DNA sequences defined in (i), (ii), (iii), or (iv) coupled to coding sequences of purification tags in order to facilitate the purification and identification of expressed peptides; and

vi) synthetic DNA sequences defined in (i), (ii), (iii), (iv), or (v) coupled to or inserted into the coding sequence of a protein;

wherein

(e) the vector DNA in the cells which have altered cell surface expression of the protein is isolated and sequenced, and

the sequences of the ribonucleic acids or peptides effecting the alteration of the phenotype of the cell(s) are deduced from the sequenced vector DNA;

and/or

(f) the ribonucleic acids or peptides effecting alteration of the phenotype of the cell(s) are used directly for isolation of a ligand molecule to said ribonucleic acids or peptides.

36. A method for identification of biologically active nucleic acids or peptides or their cellular ligands, which comprises the steps of

(a) producing a pool of appropriate vectors each containing a DNA sequence to be examined,

(b) efficiently transducing said vectors into a number of identical eukaryotic cells in such a way that each cell expresses either a single ribonucleic acid and possibly peptide encoded by the DNA sequence to be examined or a limited number of different ribonucleic acids and peptides encoded by DNA sequences to be examined, and in such a way that the expressed ribonucleic acid(s)

and peptide(s) are confined to the intracellular compartment of transduced cells,

(c) screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, and

(d) selecting and cloning cells which have altered the preselected phenotypic trait,

wherein the pool of appropriate vectors in step (a) contains totally or partly random DNA sequences selected from the group consisting of:

i) synthetic totally random DNA sequences;

ii) synthetic random DNA sequences wherein stop codons are absent;

iii) synthetic DNA sequences which encode random amino acid sequences with an even distribution of amino acids;

iv) synthetic DNA sequences defined in (i), (ii), or (iii) separated by codons which enable specific post-translational modifications of all expressed peptides or which encode anchor residues;

v) synthetic DNA sequences defined in (i), (ii), (iii), or (iv) coupled to coding sequences of purification tags in order to facilitate the purification and identification of expressed peptides; and

vi) synthetic DNA sequences defined in (i), (ii), (iii), (iv), or (v) coupled to or inserted into the coding sequence of a protein;

and wherein

(e) the vector DNA in the phenotypically altered cells is isolated and sequenced, and the sequences of the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are deduced from the sequenced vector DNA;

and/or

(f) the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are used directly for isolation of a ligand molecule to said ribonucleic acids or peptides.

37. The method according to claim 2, wherein the protein amino acid sequence is selected from an F(ab) fragment amino acid sequence and an antibody molecule amino acid sequence.

38. The method according to claim 19, wherein the restrictions consist of the presence of glycosylation sites or anchor residues.

39. The method according to claim 9, wherein the viral vector is a vaccinia virus vector.

40. In a drug development method wherein a lead compound serves as a starting point for design and synthesis of candidate drugs, the improvement comprising that a ribonucleic acid or peptide which has been identified according to claim 1 is the lead compound.

41. The method according to claim 1, wherein the ribonucleic acids or peptides effecting alteration of the preselected

phenotypic trait are used directly for isolation of a ligand molecule of the identical cells to said ribonucleic acids or peptides.

42. A method for identification of biologically active nucleic acids or peptides or their cellular ligands, which comprises the steps of

(a) producing a pool of appropriate vectors each containing a DNA sequence to be examined,

(b) efficiently transducing said vectors into a number of identical eukaryotic cells in such a way that each cell expresses either a single ribonucleic acid and possibly peptide encoded by the DNA sequence to be examined or a limited number of different ribonucleic acids and peptides encoded by DNA sequences to be examined,

(c) screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, said phenotypic trait being an observable characteristic of the identical eukaryotic cells prior to and after transduction, and

(d) selecting and cloning cells which have altered the preselected phenotypic trait,

wherein the pool of appropriate vectors in step (a) contains totally or partly random DNA sequences selected from the group consisting of:

i) synthetic totally random DNA sequences;

ii) synthetic random DNA sequences wherein stop codons are absent;

iii) synthetic DNA sequences which encode random amino acid sequences with an even distribution of amino acids;

iv) synthetic DNA sequences defined in (i), (ii), or (iii) separated by codons which enable specific post-translational modifications of all expressed peptides or which encode anchor residues;

v) synthetic DNA sequences defined in (i), (ii), (iii), or (iv) coupled to coding sequences of purification tags in order to facilitate the purification and identification of expressed peptides; and

vii) synthetic DNA sequences defined in (i), (ii), (iii), (iv) or (v) coupled to or inserted into the coding sequence of a protein;

and wherein

(e) the vector DNA in the phenotypically altered cells is isolated and sequenced, and the sequences of the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are deduced from the sequenced vector DNA;

and/or

(f) the ribonucleic acids or peptides effecting alteration of the preselected phenotypic trait are used directly for isolation of a ligand molecule to said ribonucleic acids or peptides.--

R E M A R K S

Upon entry of the above amendment claims 1-26 and 30-42 will be pending in the above-captioned application.

Support for the amendment to claim 1 are found in the specification as follows: ii) and iii) page 10, line 14, through